Contains Nonbinding Recommendations

Draft Guidance on Felbamate

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Felbamate

Form/Route: Tablets/Oral

Recommended studies: 1 study

Type of study: Fasting
Design: Multiple-dose, two-way steady-state crossover *in-vivo*
Strength: 600 mg
Subjects: Male and non-pregnant female epilepsy patients.
Additional Comments:
Please also consider the following additional safety monitoring:

a. If any evidence of bone marrow (hematologic) depression occurs, felbamate treatment should be discontinued and a hematologist consulted to ensure appropriate medical care.
b. Additional criteria for exclusion from the study relative to baseline be practiced including:
    i. two-fold increase in the highest, 2-day pre-study seizure frequency,
    ii. single generalized, tonic-clonic seizure if none occurred during pre-treatment screening, and/or,
    iii. significant prolongation of generalized, tonic-clonic seizures.

Analytes to measure: Felbamate in plasma.

1. Measurements of felbamate are requested on at least two consecutive days immediately prior to pharmacokinetic (PK)-analysis days 7 and 14 to confirm steady-state concentrations of felbamate (i.e., additional consecutive measures on days 5, 6 and 12, 13).

2. Because felbamate is rapidly absorbed and reaches a peak plasma concentration within 1-3 hours post consumption, please also include blood sampling at 0.25 hours after drug dosing to accurately measure the absorption/distribution phases of the felbamate PK profile.

3. Patients who receive multiples of 600 mg tablets of felbamate per day (1200-4800mg/day) would be eligible for the study by continuing their established maintenance dose. Because patients will be administered different dosing regimens, the dose needs to be included in the Analysis of Variance (ANOVA) statistical model. Dose normalization is not advised.

4. No washout period is necessary between treatment periods.

5. You are encouraged to submit protocols for the *in-vivo* bioequivalence studies to be conducted at steady state in patients already taking the RLD at a therapeutic dose for review prior to initiating the studies.

Bioequivalence based on (90% CI): Felbamate

Waiver request of in-vivo testing: 400 mg based on (i) acceptable bioequivalence studies on the 600 mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Dissolution test method and sampling times:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.fda.gov/cder/ogd/index.htm. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the application.